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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,977	10/04/2005	David Deperthes	KZY-002USRCE	3931

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EXAMINER	
GUSSOW, ANNE	
ART UNIT	PAPER NUMBER
1643	
MAIL DATE	DELIVERY MODE
10/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,977	DEPERTHES ET AL.	
	Examiner	Art Unit	
	ANNE M. GUSSOW	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6-10,12,17,28-30,41-46 and 49-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6-10,12,17,28-30,41-46 and 49-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/18/08, 8/26/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 18, 2008 has been entered.

2. Claims 1, 41-44, 49, and 59 have been amended.

3. Claims 1, 4, 6-10, 12, 17, 28-30, 41-46, and 49-68 are under examination.

4. The following office action contains NEW GROUNDS of Rejection.

Information Disclosure Statement

5. The information disclosure statements (IDS) submitted on August 18, 2008 and August 26, 2008 have been fully considered by the examiner and an initialed copy of the IDS is included with the mailing of this office action.

Objections Withdrawn

6. The objection to claims 1, 41, 43, 44, 49, and 59 as containing sequences without SEQ ID Nos. is withdrawn in view of applicant's amendment to the claims.

Rejections Maintained/ NEW GROUNDS of Rejection

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 49 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 49 is indefinite for reciting the phrase "humanized or human" when describing the cartilage oligomer matrix polypeptide. The term humanized is generally associated with non-human antibodies which have been modified to contain human residues in the constant and framework regions, but retain non-human residues in the CDR regions. The specification defines humanized as forms of non-human (e.g., rodent) portions of the Peptabody, especially the humanized cartilage oligomer matrix polypeptide and the portion of a hinge region of an immunoglobulin polypeptide, refer to chimeric parts thereof that contain minimal sequence derived from non human immunoglobulin (paragraph 80). It is not clear from the claim or the definition, which residues of the cartilage oligomer matrix polypeptide are human and which are non-human since the polypeptide is not an antibody with defined CDR regions. Additionally,

the specification discloses a human cartilage oligomer matrix polypeptide and one would not be able to humanize a human protein.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 4, 6-10, 12, 17, 28-30, 41-46, and 49-68 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant fusion peptabody which binds to an epidermal growth factor receptor comprising a specific portion of a cartilage oligomer matrix polypeptide (COMP 49 amino acids as shown in figure 2), a specific portion of a hinge region of an immunoglobulin polypeptide (19 amino acids from human IgA, see page 10 lines 1-5 and figure 2), an enhancer sequence, and specific epidermal growth factor receptor ligands in table 1, does not reasonably provide enablement for a recombinant fusion peptabody comprising just any portion of a cartilage oligomer matrix polypeptide, just any portion of a hinge region of an immunoglobulin polypeptide or just any epidermal growth factor receptor ligand or fragment thereof or just any fusion protein comprising an enhancer sequence (claim 41). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

> Wands states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a recombinant fusion peptabody, which binds to an epidermal growth factor receptor selected from the group consisting of ErbB-1, ErbB-3, and or ErbB-4, comprising: (a) a cartilage oligomer matrix polypeptide portion which is capable of oligomerizing; (b) a peptide enhancer sequence having an amino acid sequence selected from the group consisting of YSFE (SEQ ID NO: 5), YSFEDL (SEQ ID NO: 6), and YSFEDLYRR (SEQ ID NO: 9) and located at the N terminus of the peptabody; (c) a hinge region of an immunoglobulin polypeptide located at the C terminus of the cartilage oligomer matrix polypeptide portion; and (d) an epidermal growth factor receptor ligand which can bind to the epidermal growth factor receptor, located at the C terminus of the hinge region, wherein said recombinant fusion peptabody is capable of inducing cellular death in a cell expressing said epidermal growth factor receptor, wherein said recombinant fusion peptabody is multimeric, wherein said epidermal growth factor receptor ligand is selected from the group consisting of: (a) an epidermal growth factor polypeptide or receptor binding fragments thereof, (b) a growth blocking peptide or receptor binding fragments thereof, (c) a TGF

alpha polypeptide or receptor binding fragments thereof, (d) a plasmocyte spreading peptide or receptor binding fragments thereof, (e) a paralytic peptide or receptor binding fragments thereof, (f) a cardioactive peptide or receptor binding fragments thereof, (g) an amphiregulin polypeptide or receptor binding fragments thereof, (h) a heparin-binding epidermal growth factor-like polypeptide or receptor binding fragments thereof, (i) a betacellulin polypeptide or receptor binding fragments thereof, and or (j) a viral EGF-like polypeptide or receptor binding fragments thereof.

The claims are also broadly drawn to a fusion protein comprising an enhancer sequence comprising an amino acid sequence selected from the group consisting of: YSFE (SEQ ID NO: 5), YSFEDL (SEQ ID NO: 6), and YSFEDLYRR (SEQ ID NO: 9).

The specification discloses a recombinant fusion peptabody which binds to an epidermal growth factor receptor, comprising an enhancer, 49 amino acids of human oligomeric matrix protein, 19 amino acids of human IgA as a hinge, and a full length human epidermal growth factor (see figure 2). The specification discloses a list of specific EGF receptor ligands which have been fused to the peptabody (table 1, SEQ ID Nos. 10-29). The specification does not disclose just any receptor binding fragments as being functional in the peptabody structure. The specification does not disclose how the structure of the ligand fragment would affect the structure and/or function of the peptabody.

Regarding claim 41, the specification does not disclose fusion proteins other than the recombinant fusion peptabody. The specification does not disclose whether the

sequences of SEQ ID Nos. 5, 6, or 9 would function as an enhancer with any other protein or peptide.

Applicant's arguments filed August 18, 2008 have been carefully considered but are deemed not to be persuasive. The response states that examples 6 and 7 and Figures 25 and 26 of the instant specification describe experiments that examine enhancer sequences that are able to increase decabody and peptabody production, respectively (see response page 12). In response to this argument, applicant has demonstrated in Figures 25 and 26 that the enhancer sequences are able to increase production of a single specific construct. This construct would not be representative of a broad genus of fusion proteins which would be transcribed from any of a large number of potential promoter sequences. Applicant's specification does not disclose which promoter elements are necessary for the enhancer to function nor if the enhancer functions with a variety of promoters.

Regarding the COMP portion, Applicant's amendment to claims 43 and 59 providing the specific COMP portion sequence and the evidence provided on applicant's supplemental IDS are sufficient to overcome this part of the rejection.

Regarding the enhancer sequence, Applicant's amendment to claims 1, 43, 44, 49, and 59 are sufficient to overcome this part of the rejection.

Regarding the hinge region, Applicant's amendment to claims 43 and 59 providing the specific hinge sequence are sufficient to overcome this part of the rejection. Independent claims 1, 44, and 49 remain rejected. Applicant's arguments regarding the hinge region have been carefully considered, however, they are not

persuasive. The response states that the specification teaches that the hinge is used as a spacer between protein domains, i.e., between the COMP portion and the EGF receptor ligand of the peptabody (or monomer thereof). The specification provides an example of such a spacer, e.g., a 19 amino acid hinge derived from an Ig (see response page 16). In response to this argument, it is well known in the art that the length of spacer molecules affects protein folding for antibody molecules. Hudson and Kortt (Journal of Immunological Methods, 1999. Vol. 231, pages 177-189), teach variation in linker residues affects folding of Fv domains and can force folding into dimers and trimers. Thus, the length of a spacer is important in the structural folding of the molecules.

Regarding the ligands, applicant has disclosed specific ligand sequences that bind the EGF receptor in the structure of the peptabody. Fattah, et al. (International Journal of Cancer, 2006, as cited in a previous office action) teach that the correct formation of intra- and intermolecular disulfide bridges is challenging in creating a fusion molecule with a complex protein such as the human epidermal growth factor. Fattah, et al. also teach that human EGF forms inclusion bodies when produced in bacteria and requires denaturation and renaturation to recover biological activity (page 2460). Therefore, one of ordinary skill in the art would not predict that just any fragment of just any epidermal growth factor ligand would function in a peptabody fusion construct.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNE M. GUSSOW whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow

October 10, 2008

/David J Blanchard/
Primary Examiner, Art Unit 1643